

smokeless tobacco, switching to products with greater nicotine delivery may also contribute to nicotine dose escalation (US DHHS 1986).

Animal Studies

Animal studies have proved useful in establishing the actual development of tolerance to nicotine, the magnitude of such tolerance, and mechanisms that underlie this tolerance. The majority of these studies have used the rat and mouse as experimental subjects.

Most of the chronic tolerance studies using the rat have focused on the effects of nicotine on locomotor activity. Depression of locomotor activity typically occurs following the injection of nicotine in doses exceeding 0.2 mg/kg in drug-naive rats. Tolerance to this depression develops following chronic treatment (Keenan and Johnson 1972; Stolerman, Fink, Jarvik 1973; Stolerman, Bunker, Jarvik 1974). The magnitude of this tolerance is influenced by the dose and dosing interval. Tolerance persists for greater than 90 days when nicotine is injected chronically. Tolerance to the effects of injected nicotine on depression of locomotor activity could also be produced with nicotine administered in the rats' drinking water or through subcutaneously implanted reservoirs (Stolerman, Fink, Jarvik 1973).

Under certain experimental conditions, rats treated chronically with nicotine exhibit an increase in locomotor activity following nicotine challenge (Morrison and Stephenson 1972; BaA5ttig et al. 1976; Clarke and Kumar 1983a,b). A careful analysis of the response to an acute challenge dose of nicotine demonstrated that soon after the first dose of nicotine, depressed locomotor activity was observed; after 40 min or more, increased locomotor activity became apparent (Clarke and Kumar 1983b). Chronically injected rats exhibited this enhanced activity progressively earlier postinjection. More recently, Ksir and others (1985, 1987) demonstrated that chronic nicotine injections may result in enhanced locomotor activity immediately after nicotine injection if the rats were acclimated to the test apparatus for 1 hr before nicotine injection. These findings indicate that in the rat, tolerance develops to the depressant effects of nicotine and that this tolerance uncovers a latent stimulatory action.

If mice are injected chronically with nicotine, tolerance develops to the locomotor depressant effects elicited by a challenge dose of nicotine (Hatchell and Collins 1977). The degree and rate of development of tolerance appear to be influenced by the sex, as well as the strain, of the animals. Tolerance development has been studied by continuously infusing mice of several inbred strains with nicotine and assessing tolerance by measuring locomotor activity, body temperature, respiratory rate, heart rate, and acoustic startle response following nicotine challenge. Such studies have demonstrated that: (1) Tolerance to nicotine increases with the nicotine

infusion dose (Marks, Burch, Collins 1983a); (2) Tolerance is specific for nicotinic cholinergic agonists in that nicotine-infused animals are not cross-tolerant to the muscarinic cholinergic agonist oxotremorine (Marks and Collins 1985); (3) Maximal tolerance is attained within 4 days following the initiation of infusion and is lost within 8 days following the cessation of infusion (Marks, Stitzel, Collins 1985); (4) Tolerance development varies between inbred mouse strains, with some strains exhibiting marked tolerance and other strains showing very little (Marks, Romm et al. 1986); and (5) Mouse strains that fail to develop tolerance to nicotine are also relatively insensitive to the effects elicited by an acute injection of nicotine (Marks, Stitzel, Collins 1986). More recently these investigators compared the effects of continuous and pulse infusions of nicotine on tolerance development (Marks, Stitzel, Collins 1987). Pulse infusion was used to simulate the conditions obtained when tobacco is smoked. Although the total dose infused was the same in continuously infused and pulse-infused animals, marked differences in tolerance were seen. The pulse-infused animals exhibited a greater degree of tolerance. The degree of tolerance was most correlated with peak nicotine concentrations.

Chronic nicotine administration results in tolerance to a number of other nicotinic effects. Tolerance develops to depression of operant responding elicited by high doses of nicotine, such that after sufficient chronic treatment, enhanced rather than depressed operant responding is seen (Clarke and Kumar 1983c; Hendry and Rosecrans 1982). Attenuation of the effects of nicotine on electroencephalogram (EEG) activity is seen in the rat following chronic injection (Hubbard and Gohd 1975). These altered EEG responses paralleled the development of tolerance to behavioral effects described by these authors as "arousal." In contrast to the findings of Hubbard and Gohd (1975), other studies indicate that chronic tolerance does not develop to the behavioral stimulation effect of nicotine (Bättig et al. 1976; Morrison and Stephenson 1972; Clarke and Kumar 1983a,c). Likewise, little or no tolerance to nicotine-induced prostration after i.v. administration was observed after chronic exposure in rats (Abood et al. 1981, 1984).

In addition, tolerance has been reported to develop to nicotine-induced increases in plasma corticosterone, but not adrenal catecholamine release in rats (Balfour 1980; Van Loon et al. 1987). Anderson and colleagues (1985) studied the effects of chronic exposure to cigarette smoke on neuroendocrine function of the rat hypothalamus. These researchers observed that chronic exposure to cigarette smoke over a period of 9 days did not result in tolerance to the ability of acute intermittent exposure to cigarette smoke to reduce serum levels of prolactin, luteinizing hormone, and follicle stimulating hormone.

Mechanisms of Chronic Tolerance

Chronic tolerance to drugs may be due to an increase in the rate of drug metabolism or to a decrease in sensitivity of the tissue to the drug. Considerable differences exist among humans in the rate of nicotine metabolism (Benowitz et al. 1982). Metabolism is faster (shorter half-life) in smokers than in nonsmokers (Schievelbein et al. 1978; Kyerematen et al. 1982; Kyerematen, Dvorchik, Vesell 1983). The contribution of enhanced nicotine metabolism to the development of nicotine tolerance in humans is unclear. Studies of rats which clearly demonstrate that chronic nicotine treatment results in tolerance to nicotine also indicate that chronic nicotine administration does not increase the rate of nicotine metabolism in rats (Takeuchi, Kuroguchi, Yamaoka 1954) or mice (Hatchell and Collins 1977; Marks, Burch, Collins 1983b). These findings indicate that tolerance to nicotine primarily involves reduced sensitivity of target tissues.

Chronic tolerance to nicotine may be due to alterations in brain nicotinic receptors (see Chapter III for further discussion of nicotine receptors). At least two types of nicotinic receptors exist in rodent brain (Marks and Collins 1982). One of these receptor types may be measured with ^3H -nicotine or ^3H -acetylcholine (^3H -ACh) (Marks, Stitzel et al. 1986; Martino-Barrows and Keller 1987), while the other type may be measured with ^{125}I -bungarotoxin (BTX). The nicotine-binding site has higher affinity for nicotine than does the BTX site (Marks and Collins 1982). Chronic nicotine injection, once or twice daily for approximately 7 days, increased the number of ^3H -nicotine/ ^3H -ACh-binding sites in the brain (Ksir et al. 1985, 1987; Morrow, Loy, Creese 1985; Schwartz and Kellar 1983, 1985). This increase in nicotine-binding sites appeared to correlate with the emergence of nicotine-induced increases in locomotor activity in the rat. Studies of tolerance to nicotine in one inbred mouse strain (DBA) also demonstrated that chronic nicotine treatment elicits an increase in the number of brain nicotinic receptors as measured with both ^3H -nicotine and BTX as the ligands (Marks, Burch, Collins 1983a; Marks and Collins 1985; Marks et al. 1985, 1986; Marks, Stitzel, Collins 1985, 1986, 1987). These studies have also shown that the number of ^3H -nicotine-binding sites increases at lower doses of nicotine than do the BTX-binding sites. An increase in ^3H -nicotine binding (Marks, Burch, Collins 1983a) parallels development of tolerance to various responses during chronic infusion. In chronically infused DBA mice, tolerance acquisition and disappearance parallel the up-regulation and return to control, respectively, of brain ^3H -nicotine binding (Marks, Stitzel, Collins 1985). These findings suggest that the increase in ^3H -nicotine binding is related to the development of tolerance to nicotine. However, further studies indicate that factors other than receptor number must also be considered, because mouse

strains that do not develop tolerance to nicotine also demonstrate up-regulation of nicotinic receptors following chronic infusion (Marks et al. 1986; Marks, Stitzel, Collins 1986).

That chronic nicotine treatment results in a decrease in response to the drug (tolerance) and an increase in the number of nicotinic receptors was an unexpected finding. Marks, Burch, and Collins (1983a) and Schwartz and Kellar (1985) have suggested that chronic nicotine treatment results in chronic desensitization of nicotinic receptors. Chronic desensitization of the nicotinic receptor is comparable to chronic treatment with an antagonist and could be the stimulus for up-regulation of the receptors. According to this hypothesis, there is an increase in number of brain nicotinic receptors but a decrease in the absolute number of "activatable" (nondesensitized) receptors. This would result in a decreased response to nicotine (tolerance). Marks and coworkers suggest that inbred mouse strains failing to exhibit tolerance to nicotine, under the procedures used by these investigators, have brain nicotinic receptors that resensitize more rapidly than do those strains that do exhibit tolerance.

By treating rats chronically with the acetylcholinesterase inhibitor disulfoton, Costa and Murphy (1983) have found a decrease in rat brain ^3H -nicotine binding. Disulfoton-treated rats were also tolerant to the antinociceptive effects of nicotine. Thus, tolerance to nicotine effects may be seen when the number of nicotinic receptors is increased or decreased by chronic drug treatment. The observation that tolerance to at least one effect of nicotine can be obtained by a technique that decreases brain nicotinic receptor numbers supports the idea that chronic nicotine treatment results in an increase in the total number of receptors but a decrease in those that may be activated by nicotine; that is, a high fraction of the up-regulated receptors are desensitized.

In contrast to the studies reviewed above, some investigators have found no change in the number or affinity of ^3H -nicotine-binding sites in the brains of rats chronically exposed to nicotine (Abood et al. 1984; Benwell and Balfour 1985).

Other potential neurochemical explanations for tolerance to nicotine have been considered. Several reports (Westfall 1974; Giorguieff et al. 1977; Arqueros, Naquira, Zunino 1978; Giorguieff-Chesselet et al. 1979) indicate that nicotine stimulates dopamine release in vitro, and a recent study demonstrated that nicotinic agonists are less effective in stimulating dopamine release in slices of striatum obtained from rats that had been chronically treated with the nicotinic agonist dimethylphenylpiperazinium (DMPP) (Westfall and Perry 1986). These findings are consistent with the idea that chronic nicotinic agonist treatment results in a decrease in the absolute number of receptors that can be activated.

Pharmacodynamics of Nicotine and Cigarette Smoking

As the foregoing review has shown, the intensity of nicotine's effects is related to the dose given, the time since the last dose, and the level of preexisting or acquired tolerance. Since nicotine can produce effects that lead to further use (reinforcing effects) (Henningfield and Goldberg 1983) and can also produce effects that limit use (aversive effects, usually at higher dose levels) (Danaher 1977), the strength of the effect of a given dose can determine whether more or less nicotine will be subsequently taken. Thus, factors such as tolerance can affect the manner in which nicotine controls behavior (Chapter IV). Similarly, an individual's ability to develop tolerance to the toxic actions may be critical in determining whether smoking will occur and, if smoking is initiated, whether there will be an increase in the number of cigarettes consumed each day.

Pharmacodynamic considerations may help explain the pattern of cigarette smoking throughout the day. Intervals between smoking cigarettes may be determined at least in part by the time required for tolerance to disappear. With regular smoking there is accumulation of nicotine in the body resulting in a greater level of tolerance. Transiently high brain levels of nicotine following smoking individual cigarettes may partially overcome tolerance. But the effects of individual cigarettes tend to lessen throughout the day. Overnight abstinence allows considerable resensitization to effects of nicotine, and the daily smoking cycle begins again.

Pharmacodynamic observations with i.v. dosing of nicotine explain the pattern of cardiovascular changes observed in cigarette smokers. That brief infusions of nicotine increase heart rate to a maximum suggests that heart rate will increase most with the first few cigarettes of the day, but subsequently will not vary in relation to the amount of nicotine consumed. That only partial tolerance develops to heart rate acceleration due to nicotine suggests that effects on heart rate may persist as long as significant levels of nicotine persist, including overnight. These predictions were confirmed in a study in which volunteer cigarette smokers smoked either high- or low-yield nonfilter research cigarettes or abstained from smoking (Benowitz, Kuyt, Jacob 1984). Full compensation for the low-yield research cigarettes, which contained only small amounts of nicotine, was impossible. Resultant nicotine blood levels were different by fourfold. As predicted, heart rate (assessed by continuous ambulatory electrocardiogram (EKG) monitoring) increased in the morning—more on smoking than nonsmoking days—and the increase occurred with the first few cigarettes of the day. Subsequently, heart rate followed a normal circadian pattern, but was always higher during smoking than during abstinence. Also, as predicted, heart rate was no different during the smoking of low-

yield or high-yield cigarettes, despite the fourfold difference in blood nicotine concentration.

Pharmacodynamic aspects of the actions of nicotine may explain in part how cigarette smoking causes coronary heart disease (US DHHS 1983). As noted before, because of the accumulation of nicotine and its dose-response characteristics, heart rate is increased during cigarette smoking for 24 hr a day. Plasma catecholamine concentrations and urinary catecholamine excretion remain increased as well (Benowitz 1986c), consistent with the theory that cigarette smoking produces sympathetic neural activation 24 hr each day. Persistent sympathetic activation could result in the following effects: (1) Alteration in lipid metabolism, resulting in a more atherogenic lipid profile; (2) Promotion of platelet aggregation and hypercoagulability; (3) Induction of vasoconstriction and coronary spasm; and (4) Increased heart rate and myocardial contractility, thereby an increase in the oxygen demands of the heart and of circulating catecholamines, which can promote cardiac arrhythmias. These factors could accelerate atherosclerosis and contribute to acute myocardial infarction in a person with preexisting coronary atherosclerosis (Benowitz 1986a) (see also Appendix B). There is no apparent correlation between acute coronary events and the time at which a person smokes a cigarette, perhaps because of the persistent effects of nicotine throughout the day.

Constituents of Tobacco Smoke Other Than Nicotine With Potential Behavioral Effects

Tobacco smoke contains more than 4,000 constituents, many of which may have biological activity (US DHHS 1983). Although nicotine is the major pharmacologic factor which determines the use of tobacco, other constituents may also be involved. The behavioral effects of tobacco constituents other than nicotine are described in the Section below and in Chapter IV. This Section focuses more on the chemicals that may be involved, whereas Chapter IV focuses more on cigarette smoking behavior.

Minor Tobacco Alkaloids

Most of the research on the minor tobacco alkaloids has been directed to determining physiological effects, such as the effect on blood pressure and other cardiovascular responses and toxicological effects, rather than the potential for behavioral effects. The pharmacologic effects of alkaloids of the nicotine group have been discussed by Bovet and Bovet-Nitti (1948) and Clark, Rand, and Vanov (1965). Nornicotine and anabasine were found to have qualitatively similar actions but to be less potent than nicotine. Larson and Haag (1943)

reported that the potency of nornicotine as determined by effects on blood pressure in dogs was about one-twelfth that of nicotine.

Nicotine analogs have been studied for discriminative stimulus effects by using animal models (Chance et al. 1978) (see also Chapter IV). The only chemical shown to produce a positive response in that test system was 3-methylpyridylpyrrolidine. Recent research has focused on binding at specific brain receptor sites. Martin and coworkers compared binding characteristics of nicotine-related compounds (Martin et al. 1986; Sloan et al. 1985). Lobeline, anabasine, and cytisine were evaluated for effects on heart rate, blood pressure, respiration rate, minute volume, and tidal volume (Sloan et al. 1987). Lobeline and anabasine bound to low-affinity sites in the brain, whereas cytisine bound only at a high-affinity site. The binding data are consistent with the pharmacologic data, indicating that lobeline and anabasine have different pharmacologic actions than cytisine. Kanne and others (1986) and Abood and Grassi (1986) evaluated two nicotine analogs, including a new radioligand, to study brain nicotinic receptors. Kachur and others (1986) studied the pharmacologic effects of a bridged-nicotine analog (methylene bridge between the methyl of the pyrrolidine ring and the α -position of the pyridine ring). The magnitude of pressor effect depended on the particular enantiomer and dosage. These results emphasize that compounds other than nicotine may act at the nicotine receptors; however, there may be subpopulations of receptors to which different agonists and antagonists bind (Chapter III).

N-Methylated derivatives of nicotine, including nicotine isomethonium ion (N-methylnicotinium ion, NMN), have been shown to have pressor and neuromuscular effects in some species (Shimamoto et al. 1958). Nicotine isomethonium ion was first reported to be a metabolite of nicotine present in smokers' urine by McKennis and coworkers in the 1960s, and its presence in smokers' urine has been recently confirmed (Neurath et al. 1987). Recently Crooks and coworkers (Cundy, Godin, Crooks 1985) have shown that only the (R)-isomer of nicotine is converted to nicotine isomethonium ion in vitro in guinea pig tissue homogenates or in vivo in guinea pigs. Consequently, it is uncertain as to whether the nicotine isomethonium ion present in smokers' urine arrives from the small amount of (R)-nicotine present in tobacco smoke, or whether the human enzyme systems have different specifications than the guinea pig enzymes. Because little if any nicotine isomethonium ion penetrates the blood-brain barrier (Pool 1987; Aceto et al. 1983), it would appear that this metabolite could have behavioral actions only if it were formed in the CNS. These findings emphasize the complexity of the pharmacology of nicotine-related compounds. It can be concluded from research on these compounds that some do bind to specific brain receptors and may result in centrally mediated physiological changes. However,

there is inadequate evidence to date that any of these compounds produces either aversive or rewarding effects in human smokers.

"Tar" and Selected Constituents of Tobacco Smoke Which Contribute to Taste and Aroma

"Tar" is used to describe the dry particulate matter without the nicotine in tobacco smoke (Pillsbury et al. 1969). The possible role of tar in the maintenance of the cigarette smoking habit has been considered. Goldfarb and coworkers (1976) studied the effects of the tar content (determined by cigarette smoking machine testing) on the subjective reactions to cigarette smoking. Ratings of strength were not related to the tar index of the cigarettes. The results were interpreted as indicating that tar did not have a role in the maintenance of cigarette smoking behavior. In a later study, Sutton and coworkers (1982) found that when nicotine yield was held constant, smokers of lower-tar cigarettes puffed more smoke and had higher drug plasma levels. These results suggested that smokers were compensating for reduced delivery of tar by inhaling a greater volume of smoke. Because these two studies used different experimental designs, it is difficult to draw a conclusion as to the role of tar in relation to smoking behavior. However, based on knowledge about the taste and aroma constituents of cigarette smoke, it is likely that some of the chemicals in the tar fraction contribute to tobacco use, if only by providing distinct sensory stimuli (Chapter VI). Consistent with this possibility, minimal levels of tar are held by tobacco manufacturers to be important to the taste characteristics of tobacco smoke.

Several thousand compounds have been isolated from tobacco and tobacco smoke (Dube and Green 1982), and many of these may be biologically active (IARC 1986). The precursors to the carotenoids and diterpenoids, selected nitrogenous and sulfur constituents, waxes and lipids, and phenolics and acids contribute to the taste and aroma of tobacco (Enzell and Wahlberg 1980; Heckman et al. 1981; Davis, Stevens, Jurd 1976). A number of the isoprenoid compounds that influence the taste and aroma of smoke may be formed by sequential oxidation, rearrangement, and reduction reactions (Davis, Stevens, Jurd 1976). Enzell and Wahlberg (1980) described several norisoprenoid compounds which are derived from the cyclic carotenoids and are important to smoke aroma. The particular taste and aroma of a cigarette can be influenced by the selection of the grade (quality and leaf position on the plant) and type of tobacco used in the blend.

Taste and smell receptors in the pharynx, larynx, and nose provide the first sensory input to the smoker as he or she lights up, an experience which is generally perceived as pleasurable (Rose et al. 1985). The taste and smell of tobacco smoke may be important

reinforcers for tobacco smoking (Jarvik 1977)—at least following repeated association with the reinforcing effects of nicotine administration (Chapter VI). By such behavioral conditioning, sensory cues provided by tar and flavor additives could come to control the tobacco-consuming behavior of the tobacco user. Changes in smoking patterns when brands are switched and brand selection may be a response in part to the particular flavor and aroma of the product (Thornton 1978).

Carbon Monoxide

The mainstream and sidestream carbon monoxide (CO) deliveries of cigarettes are influenced by cigarette design and puffing characteristics of the smokers. Depending upon these factors, the mainstream delivery usually ranges from 10 to 20 mg/cigarette. In a study of 29,000 blood donors in 18 locations around the United States, smokers were found to have median carboxyhemoglobin (COHb) levels ranging from 3.2 to 6.2 percent (Stewart et al. 1974). Anderson, Rivera, and Bright (1977) found the COHb levels in 50 smokers to vary from 3.9 to 14.0 percent, with the mean of 8.1 percent. The mean increment in COHb immediately after smoking 1 cigarette was 0.64 percent. COHb levels gradually decrease in blood after cessation of smoking. Carbon monoxide is eliminated in expired air. The rate of elimination depends on pulmonary blood flow and ventilation. The half-life of COHb is 2 to 4 hr during daytime hours, but as COHb is related to the level of exercise, the half-life may be as long as 8 hr during sleep (Wald et al. 1975). For these reasons, many smokers awaken in the morning with substantial levels of COHb, despite not smoking overnight (Benowitz, Kuyt, Jacob 1982). Persons smoking cigarettes with lower nicotine and CO yields have only slightly lower levels of COHb when compared with those smoking higher-yield products (Wald et al. 1980, 1981; Sutton et al. 1982; Hill, Haley, Wynder 1983; Benowitz, Jacob, Yu et al. 1986).

Benowitz and colleagues (1986) studied tar, nicotine, and CO exposure in smokers switched from their usual brand to low-, high-, and ultra-low-yield cigarettes. This study indicated that there were no differences in exposure comparing low- and high-yield, but tar and nicotine exposure were reduced by about 50 percent and CO by 36 percent while smoking *ultra*-low-yield cigarettes. Switching from a high to lower yield cigarette does not significantly reduce blood COHb although switching to ultra low cigarettes has been shown to lead to a significant reduction.

The toxic effects of high CO levels are well documented (US DHHS 1983). Some studies have tried to determine whether CO levels in the blood similar to those observed in smokers can affect behavior. Beard and Wertheim (1967) and Wright, Randell, and Shephard (1973) reported performance decrements with COHb levels below 5.0

percent; however, Guillerman, Radziszewski, and Caille (1978) found no psychomotor performance effects at COHb levels of 7 and 11 percent. Thus, the data are inconclusive with regard to the possible influence of CO on psychomotor performance at levels normally encountered in smokers.

Acetaldehyde and Other Smoke Constituents

Acetaldehyde is a major constituent of tobacco smoke, with mainstream smoke levels in commercial cigarettes ranging from 0.5 to 1.2 mg/cigarette (IARC 1986). The delivery of volatile aldehydes is influenced by cigarette design, with reductions achieved by specific filtration and air dilution techniques. Yields over 5.9 mg have been reported for large cigars (Hoffmann and Wynder 1977). Acetaldehyde is the primary metabolite of ethanol, and its toxic potency is 20 to 30 times that of ethanol. Acetaldehyde has been suggested to have an adverse effect on the heart (James et al. 1970). Acetaldehyde and acrolein, another important aldehyde in the gas phase of cigarette smoke, activate the sympathetic nervous system (Egle and Hudgins 1974). Acetaldehyde, by releasing norepinephrine, results in a pressor effect (Kirpekar and Furchgott 1972; Green and Egle 1983). Depressor effects occur at high doses of the aldehydes in guanethidine-pretreated hypertensive rats. Frecker (1983) indicated that condensation products of acetaldehyde may be active on endogenous opioid systems. Torreilles, Guerin, and Previero (1985) reviewed the synthesis and biological properties of beta-carbolines, the condensation products of tryptophan and indole alkylamines with aldehydes. Beta-carbolines occur as plant constituents, including minor constituents in tobacco. For example, harman (1-methyl- β -carboline) has been identified in tobacco and tobacco smoke (Snook and Chortyk 1984). Carbolines from other plant species have been used as hallucinogens. The research conducted to date indicates a potential pharmacologic effect of the aldehydes, especially with regard to cardiovascular physiology; however, the evidence is inadequate to determine if these volatile smoke constituents in the doses delivered in tobacco smoke contribute to the behavioral effects of cigarette smoking.

Summary and Conclusions

1. All tobacco products contain substantial amounts of nicotine and other alkaloids. Tobaccos from low-yield and high-yield cigarettes contain similar amounts of nicotine.
2. Nicotine is absorbed readily from tobacco smoke in the lungs and from smokeless tobacco in the mouth or nose. Levels of nicotine in the blood are similar in people using different forms of tobacco. With regular use, levels of nicotine accumulate in

the body during the day and persist overnight. Thus, daily tobacco users are exposed to the effects of nicotine for 24 hr each day.

3. Nicotine that enters the blood is rapidly distributed to the brain. As a result, effects of nicotine on the central nervous system occur rapidly after a puff of cigarette smoke or after absorption of nicotine from other routes of administration.
4. Acute and chronic tolerance develops to many effects of nicotine. Such tolerance is consistent with reports that initial use of tobacco products, such as in adolescents first beginning to smoke, is usually accompanied by a number of unpleasant symptoms which disappear following chronic tobacco use.

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CHAPTER III

NICOTINE: SITES AND MECHANISMS OF ACTIONS